Short communication

Incidence of infectious morbidity events after second-line antiretroviral therapy initiation in HIV-infected adults in Yaoundé, Cameroon

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Background: Since antiretroviral therapy (ART), HIV-infected individuals experience mainly non-AIDS-related conditions, among which infectious events are prominent. We aimed to estimate incidence and describe overall spectrum of infectious events, including all grade events, among HIV-1-infected adults failing first-line ART in Yaoundé, Cameroon.

Methods: All patients from Cameroon enrolled in the second-line ART 2LADY trial (ANRS12169) were included in this secondary analysis. Medical files were reviewed with predefined criteria for diagnosis assessment. Incidence rates (IR) were estimated per 100 person-years (% PY).

Results: A total of 302 adult patients contributing 840 PY experienced 596 infectious events (IR 71% PY). Only 29 (5%) events were graded as severe. Most frequent infections were upper respiratory tract infections (15% PY), diarrhoea (9% PY) and malaria (9% PY). A total of 369 (62%) infections occurred during the first year (IR 130% PY) followed by a persistent lower incidence during the following 3 years. Higher IR were observed in patients with CD4$^+$ T-cell count <200 cells/mm^3 for all infectious events except for mycobacterial and parasitic infections. IR of viral, bacterial and parasitic infectious events were lower in case of co-trimoxazole use in patients with CD4$^+$ T-cell count <200 cells/mm^3.

Conclusions: Infectious events are common and mainly occur during the first year after treatment initiation. Second-line ART initiation had a positive impact on the entire spectrum of infectious morbidity.

Introduction

By the end of 2013, almost 13 million people in low- and middle-income countries (LMICs) were receiving antiretroviral therapy (ART), and the African World Health Organization (WHO) region accounted for 7.5 million of treated patients [1,2]. ART has led to a major decrease in AIDS-related morbidity and mortality in LMICs [3–5] and, nowadays, non-AIDS events, driven by infectious morbidity events, account for the largest part of the encountered morbidity of HIV-infected individuals [6–9]. Most reports describing non-AIDS-related morbidity focus on severe events or on specific events, such as bacterial infectious events, and they usually focus either on untreated HIV-infected subjects or on patients initiating ART [6–11].

The present study aims to further document infectious morbidity in HIV patients from LMIC settings. The objectives were to estimate incidence and describe overall spectrum of infectious events, including all grade events, among HIV-1-infected adults failing standard first-line ART who were enrolled in a second-line clinical trial in Cameroon. Secondary objectives include description of trends over time, as well as estimation of CD4$^+$ T-cell count- and co-trimoxazole use-specific incidence rates.

Methods

Patients and follow-up

We conducted a secondary analysis of the ANRS 12169-2LADY study [12], a prospective, randomized trial conducted in three African cities (Yaoundé, Cameroon; Dakar, Senegal; Bobo Dioulasso, Burkina Faso) to compare efficacy of three second-line regimens (tenofovir disoproxil fumarate [TDF], emtricitabine [FTC], ritonavir-boosted lopinavir [LPV/r]; abacavir [ABC], didanosine [ddI] LPV/r; TDF/FTC, ritonavir-boosted darunavir [DRV/r]). It enrolled HIV-1-infected adults, failing a non-nucleoside reverse transcriptase inhibitor-based first-line ART, defined as a confirmed HIV-1 viral load above 1,000 copies/ml after 1 month of adherence support. For the purpose of that study, data were limited to patients from Yaoundé, owing the geographical heterogeneity of infectious morbidity spectrum between west and central Africa. The Institutional Ethics Committee of the Institut de Recherche pour le Développement in France and the countries' national Ethics Committees approved the protocol. All participants provided written informed consent.

Follow-up visits were scheduled every 3 months during the first year and every 6 months thereafter. Clinical evaluation, HIV-1 viral load and CD4$^+$ T-cell count measurements were performed at all scheduled visits. Non-scheduled consultations were available at any time if needed, and all care, drugs, laboratory testing or imaging were free of charge.

Definitions and classification of infectious morbidity events

The primary outcome was the occurrence of new infectious events and thus only events occurring during the follow-up period (from inclusion to June 2014) were considered. Ongoing events at the time of inclusion were not considered. Infectious events were classified using the 10th revision of the WHO International Classification of Diseases [13]. All participants' medical files were reviewed and all events were retrospectively validated by two experienced infectious diseases physicians (AG, LC) using predefined standardized definitions, and classified in five broad categories: fungal infections, viral infections, bacterial infections, parasitic infections and mycobacterial infections (Additional file 2). AIDS-defining events were defined as Center for Disease Control stage C events [14]. Severe infectious events were defined as infectious events graded 3 or 4 using the ANRS scale of morbidity events [15].

Statistical analysis

The incidence rate (IR) was defined as the number of events divided by the number of person-years (PY) at risk, and was expressed per 100 PY (% PY) of follow-up. All participants were considered at risk for all the events until the study termination date or until last visit date if censored. Participants were censored if they died, were lost to follow-up or transferred to another clinic. Recurrences were considered if at least 1 month elapsed between two episodes, with a disease-free interval.

IR were estimated for 4 successive years of follow-up (year 1–4), for three CD4$^+$ T-cell count categories (<200 cells/mm^3, 200–349 cells/mm^3 and ≥350 cells/mm^3) and according to co-trimoxazole use, using cumulative time spent in each period, or in each CD4$^+$ T-cell count or co-trimoxazole use strata. The current CD4 value assigned to each time interval corresponded to the CD4$^+$ T-cell count of the most recent previous dosage.

Results

Patients and follow-up

Between January 2010 and September 2012, 302 out of 454 patients were included in the Cameroon's sites of the ANRS 12169-2LADY trial and followed until June 2014. The cumulative follow-up was 840 PY, with a median of 2.8 years per patient (Table 1). The median CD4$^+$ T-cell count increased from 160 cells/mm^3 at baseline to 436 cells/mm^3 at 48 months. A total of 13 (4%) patients were switched to a third-line ART.

AIDS-defining and WHO-classifying events

Sixteen patients experienced 18 AIDS-related events. Two were non-infectious while 16 were infectious events. IR was 2.1% PY, and remained stable over time. Thirty-eight WHO 3 or 4 classifying events occurred over the entire study period with an IR of 4.5% PY.

Overall incidence rates and changes over time

Over the entire study period, a total of 596 infectious events were reported. Out of 302 patients, 234 (78%) experienced at least one infectious event. Median number of events per patient was 2. Only 29 (5%) events were graded as severe. The most common events were viral infections (26.7% PY, mainly upper respiratory tract infections [14.9% PY]), bacterial infections (21.8% PY, mainly diarrhoea [8.9% PY]) and malarial accesses (8.6% PY; Table 2).

A decrease of the IR over the 4 years of follow-up was observed for most infections: the IR for overall infectious events decreased from 129.5% PY (116.9–143.4) in the first year to 43.5% PY (31.3–60.3) in the fourth year, fungal infections from 20.4% PY (15.7–26.3) to 1.2% PY (0.2–8.6), viral infections from 55.1% PY (47.1–64.4) to 14.5% PY (8.2–25.5) and bacterial infections from 37.2% PY (30.7–45.0) to 15.7% PY (9.1–27.0; Figure 1; Additional file 3). Furthermore,

Table 1. Baseline and follow-up characteristics of the 302 participants

Characteristics	Value
Baseline	
Women, *n* (%)	217 (72)
Median age, years (IQR)	38 (33–47)
CD4+ T-cell count, cells/mm^3 (IQR)	160 (68–280)
CD4+ T-cell count	
<200 cells/mm^3, *n* (%)	185 (61)
200–349 cells/mm^3, *n* (%)	76 (25)
≥350 cells/mm^3, *n* (%)	41 (14)
Median HIV-1 viral load, $\log_{10}$ copies/ml (IQR)	4.6 (4.2–5.1)
WHO classification at baseline	
1, *n* (%)	269 (89)
2, *n* (%)	16 (5)
3, *n* (%)	12 (4)
4, *n* (%)	5 (2)
WHO classification at ART initiation	
1, *n* (%)	56 (19)
2, *n* (%)	63 (21)
3, *n* (%)	140 (46)
4, *n* (%)	43 (14)
Median first-line ART duration, months (IQR)	53 (37–71)
Co-trimoxazole prophylaxis, *n* (%)	243 (80)
Second-line regimen	
TDF/FTC LPV/r, *n* (%)	101 (33)
ABC ddI LPV/r, *n* (%)	99 (33)
TDF/FTC DRV/r, *n* (%)	102 (34)
Follow-up	
Time of follow-up	
Median, years (IQR)	2.8 (2.0–3.5)
Cumulative, person-years	840
Followed until study termination (11 June 2014), *n* (%)	272 (90)
Discontinued, *n* (%)	30 (10)
Deceased, *n* (%)	9 (3)
Lost to follow-up, *n* (%)	14 (5)
Transferred, *n* (%)	6 (2)
Withdrawn, *n* (%)	1 (0)

ABC, abacavir; ddI, didanosine; DRV/r, ritonavir-boosted darunavir; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; TDF, tenofovir disoproxil fumarate.

the most important decrease was observed in the first trimesters after initiation of second-line ART. The IR fell from 244.2% PY (210.6–283.6) to 93.7% PY (73.7–119.0) from the first to second trimester.

CD4-specific incidence rates

Higher IRs were observed in patients with CD4+ T-cell count <200 cells/mm^3 (Table 2). When comparing IRs between CD4 strata ≥350 cells/mm^3 and CD4 <200 cells/mm^3, the percentage of decrease of the IR was 55% for overall infectious events, 71% for fungal infections, 66% for viral infections and 53% for bacterial infections. IRs for mycobacterial and parasitic infections by CD4 strata were similar (Table 2).

Effect of co-trimoxazole use

IR for overall infectious events in co-trimoxazole non-users was 56.3% PY (48.6–65.1), whereas it was higher (80.0% PY [72.6–88.1]) in co-trimoxazole users. However, in the CD4+ T-cell count <200 cells/mm^3 strata, IR was 102.4% PY (88.0–119.1) and 215.8% PY (162.6–286.4) in co-trimoxazole users and non-users, respectively. This was true for all subgroups, with the exception of fungal and mycobacterial infections. In CD4+ T-cell count 200–349 cells/mm^3, IRs were similar for co-trimoxazole users and non-users (66.0% PY [56.7–76.8] versus 62.0% PY [43.6–88.1], respectively) and became significantly higher in co-trimoxazole users in the CD4+ T-cell count >350 cells/mm^3 strata (78.6% PY [63.1–97.8] versus 40.9% PY [33.7–49.6] in non-users).

Discussion

We report infectious morbidity data from 302 adult patients after initiation of efficient second-line ART in Yaoundé, Cameroon. Although participants were experiencing first-line ART failure and had a median CD4+ T-cell count at inclusion below 200 cells/mm^3, few AIDS-related, WHO-classifying and severe infectious events were observed. Compared with previous studies in patients under first-line ART, IRs of WHO-classifying 3 and 4 events were lower in our patients (4.5% PY versus 10.7% PY, respectively) [5], as were the IR of non-severe bacterial events and tuberculosis [9].

IRs of most infectious events (except parasitic infections) strongly decreased over the study period and the largest decrease occurred within the first year. Such finding have been previously reported for AIDS-defining and severe morbidity events [3,5], with an initial strong decrease in the IR during the first months following ART initiation. Immune reconstitution could partially explain this decline; it has been shown to be a protective factor for the occurrence of opportunistic AIDS-defining conditions [3,11] and, to a lesser degree, for non-AIDS-defining infections such as bacterial [16,17], viral [17] and parasitic [17,18] infections. Our results suggest that a higher CD4+ T-cell count is also a protective factor for overall infectious morbidity, and not only for severe-graded events.

Our study also supports the beneficial effect of co-trimoxazole prophylaxis, consistently with previous reports [19–22]. This was true at least in participants with CD4+ T-cell count <200 cells/mm^3 but for most infectious events; IR were much lower in case of co-trimoxazole use in this CD4 strata. However, this result was not confirmed among patients with CD4+ T-cell counts between 200 and 349 cells/mm^3 and an inverse association was found among patients with CD4+ T-cell count ≥350 cells/mm^3 (higher IRs in

Table 2. Overall and CD4-specific IRs (per 100 person-years) for all infectious events in adults receiving second-line ART (*n*=302)

	Events		Global (840 PY)	CD4<200 (186 PY)		200<CD4< 350 (303 PY)		CD4≥350 (350 PY)	
	All events	Presumptive[a]	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)
Global	596 (100)	494 (83)	71.0 (65.5–76.1)	217	116.5 (102.0–133.0)	198	65.3 (56.9–75.1)	181	51.7 (44.7–59.8)
Severe events	29 (5)	16	3.5 (2.4–5.0)	12	6.4 (3.7–11.3)	9	3.0 (1.5–5.7)	8	2.3 (1.1–4.6)
Fungal infections	81 (13)	74	9.7 (7.8–12.0)	36	19.3 (13.9–26.8)	25	8.3 (5.6–12.2)	20	5.7 (3.7–8.8)
Oral and oesophageal candidiasis	7 (1)	7	0.8 (0.4–1.8)	6	3.2 (1.4–7.2)	1	0.3 (0.0–2.3)	0	0.0 (NC)
Genital candidiasis	45 (7)	39	5.4 (4.0–7.2)	21	11.3 (7.3–17.3)	13	4.3 (2.5–7.4)	11	3.1 (1.7–5.7)
Dermatophytosis	28 (5)	28	3.3 (2.3–4.8)	8	4.3 (2.1–8.6)	11	3.6 (2.0–6.6)	9	2.6 (1.3–4.9)
Other	1 (0)	0	0.1 (0.0–0.9)	1	0.5 (0.1–3.8)	0	0.0 (NC)	0	0.0 (NC)
Viral infections	224 (38)	224	26.7 (23.4–30.4)	85	45.6 (36.9–56.4)	85	28.1 (22.7–34.7)	54	15.4 (11.8–20.1)
Upper respiratory tract infections	125 (21)	125	14.9 (12.5–17.7)	46	24.7 (18.5–33.0)	46	15.2 (11.4–20.3)	33	9.4 (6.7–13.2)
Flu–like syndrome	51 (9)	51	6.1 (4.6–8.0)	18	9.7 (6.1–15.3)	17	5.6 (3.5–9.0)	16	4.6 (2.8–7.5)
Herpes zoster	13 (2)	13	1.5 (0.9–2.7)	2	1.1 (0.3–4.3)	8	2.6 (1.3–5.3)	3	0.9 (0.3–2.7)
Other herpetic infections	26 (4)	26	3.1 (2.1–4.5)	13	7.0 (4.1–12.0)	12	4.0 (2.2–7.0)	1	0.3 (0.0–2.0)
Other	9 (2)	9	1.1 (0.6–2.1)	6	3.2 (1.4–7.2)	2	0.7 (0.2–2.6)	1	0.3 (0.0–2.0)
Bacterial infections	183 (31)	140	21.8 (18.9–25.2)	66	35.4 (27.8–45.1)	58	19.1 (14.8–24.8)	59	16.8 (13.0–21.7)
Pneumonia	11 (2)	0	1.3 (0.7–2.4)	3	1.6 (0.5–5.0)	3	1.0 (0.3–3.1)	5	1.4 (0.6–3.4)
Severe bacterial infections (excluding pneumonia)	7 (1)	6	0.8 (0.4–1.8)	5	2.7 (1.1–6.4)	1	0.3 (0.0–2.3)	1	0.3 (0.0–2.0)
Urinary tract infections	18 (3)	6	2.1 (1.4–3.4)	5	2.7 (1.1–6.4)	7	2.3 (1.1–4.8)	6	1.7 (0.8–3.8)
Sexually transmitted infections	18 (3)	5	2.1 (1.4–3.4)	8	4.3 (2.1–8.6)	6	2.0 (0.9–4.4)	4	1.1 (0.4–3.0)
Skin infections	44 (7)	44	5.2 (3.9–7.0)	11	5.9 (3.3–10.7)	12	4.0 (2.2–7.0)	21	6.0 (3.9–9.2)
Infectious diarrhoea	75 (13)	73	8.9 (7.1–11.2)	31	16.6 (11.7–23.7)	26	8.6 (5.8–12.6)	18	5.1 (3.2–8.2)
Other	10 (2)	6	1.2 (0.6–2.2)	3	1.6 (0.5–5.0)	3	1.0 (0.3–3.1)	4	1.1 (0.4–3.0)
Parasitic infections	98 (16)	53	11.7 (9.6–14.2)	25	13.4 (9.1–19.9)	28	9.2 (6.4–13.4)	45	12.8 (9.6–17.2)
Malarial access	72 (12)	33	8.6 (6.8–10.8)	17	9.1 (5.7–14.7)	22	7.3 (4.8–11.0)	33	9.4 (6.7–13.2)
Definitive	39 (7)	–	4.6 (3.4–6.4)	8	4.3 (2.1–8.6)	10	3.3 (1.8–6.1)	21	6.0 (3.9–9.2)
Loiasis	5 (1)	2	0.6 (0.3–1.4)	2	1.1 (0.3–4.3)	2	0.7 (0.2–2.6)	1	0.3 (0.0–2.0)
Scabies	18 (3)	18	2.1 (1.4–3.4)	6	3.2 (1.4–7.2)	3	1.0 (0.3–3.1)	9	2.6 (1.3–4.9)
Other	3 (1)	0	0.4 (0.1–1.1)	0	0.0 (NC)	1	0.3 (0.0–2.3)	2	0.6 (0.1–2.3)
Mycobacterial infections	10 (2)	3	1.2 (0.6–2.2)	5	2.7 (1.1–6.4)	2	0.7 (0.2–2.6)	3	0.9 (0.3–2.7)
Pulmonary tuberculosis	5 (1)	1	0.6 (0.3–1.4)	2	1.1 (0.3–4.3)	1	0.3 (0.0–2.3)	2	0.6 (0.1–2.3)
Extrapulmonary tuberculosis	5 (1)	2	0.6 (0.3–1.4)	3	1.6 (0.5–5.0)	1	0.3 (0.0–2.3)	1	0.3 (0.0–2.0)

Events are presented as *n* or *n* (%). [a]Diagnosis considered as presumptive using the predefined validation grid (see *Methods*). An infectious event was qualified as presumptive if it was diagnosed only on clinical features or as definitive if it was confirmed by radiological or microbiological data. ART, antiretroviral therapy; IR, incidence rate; NC, not calculated; PY, person-years.

case of co-trimoxazole use). This observation is likely to be linked to an indication bias, as co-trimoxazole prophylaxis in Cameroon is recommended until the threshold of 350 cells/mm^3 [23]. In the CD4$^+$ T-cell count ≥350 cells/mm^3 strata, participants remaining under co-trimoxazole prophylaxis were probably those experiencing infectious events and who continued therefore prophylaxis. Further investigation is needed to evaluate the benefit of such prophylaxis in patients with moderate to high level of CD4$^+$ T-cell count.

In conclusion, this study provides a detailed description of the nature and IRs of all types of infectious events in HIV patients from an African setting and highlights the positive effect of an effective second-line ART regimen on the entire spectrum of infectious morbidity.

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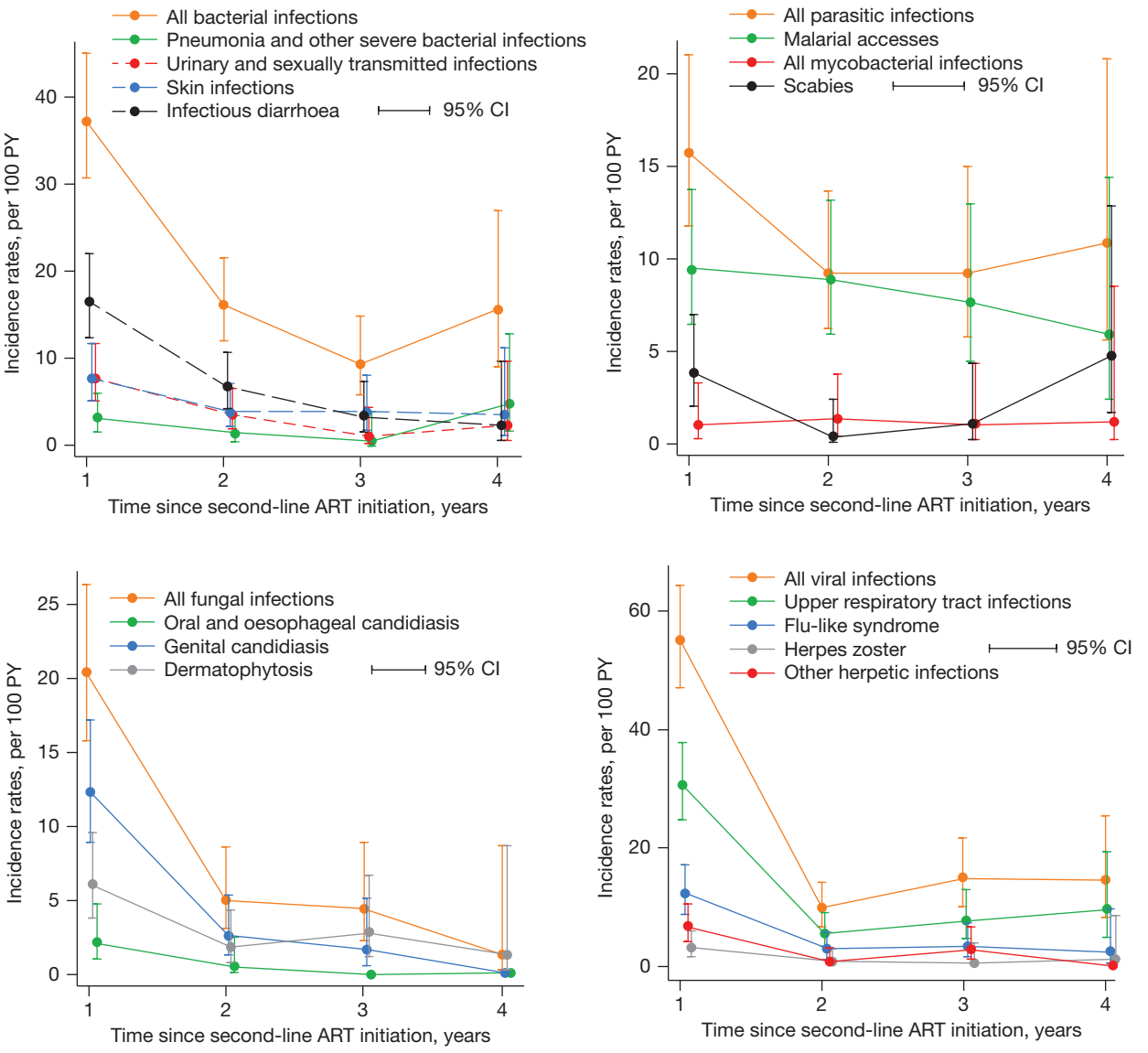
AG, LC, ED and AC contributed to the conception and design of the study, overviewed the conduct of the project and data collection, and participated in the interpretation of the data and critical revision of the manuscript. VLM contributed to the analysis and the interpretation of the data and in critical revision of the manuscript. AG, AC and SED analysed all the data, prepared figures and tables and participated in the interpretation of the data. All authors gave the final approval for this version of the manuscript.

Figure 1. Observed incidence rates over time after second-line ART initiation by subgroups of diseases



ART, antiretroviral therapy; PY, person-years.

Disclosure statement

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Additional files

Additional file 1: A list of the 2LADY study group members can be found at https://www.intmedpress.com/uploads/documents/3750_Galy_Addfile1.pdf

Additional file 2: A table showing the diagnostic criteria used by the event validation group can be found at https://www.intmedpress.com/uploads/documents/3750_Galy_Addfile2.pdf

Additional file 3: A table showing the overall and time-specific IRs for all infectious events in adults receiving second-line ART can be found at https://www.intmedpress.com/uploads/documents/3750_Galy_Addfile3.pdf

References

1. UNAIDS. The GAP report. 2015. (Accessed 6 June 2015.) Available from http://issuu.com/unaids/docs/20140716_unaids_gap_report.
2. WHO. Global update on HIV treatment 2013: results, impact and opportunities. (Accessed 14 May 2015.) Available from http://www.who.int/hiv/pub/progressreports/update2013/en/
3. De Beaudrap P, Etard JF, Diouf A, *et al*. Incidence and determinants of new AIDS-defining illnesses after HAART initiation in a Senegalese cohort. *BMC Infect Dis* 2010; **10:**179.
4. Domingues CS, Waldman EA. Causes of death among people living with AIDS in the pre- and post-HAART eras in the City of Sao Paulo, Brazil. *PLoS ONE* 2014; **9:**e114661.
5. Moh R, Danel C, Messou E, *et al*. Incidence and determinants of mortality and morbidity following early antiretroviral therapy initiation in HIV-infected adults in West Africa. *AIDS* 2007; **21:**2483–2491.
6. Abo Y, Minga A, Menan H, *et al*. Incidence of serious morbidity in HIV-infected adults on antiretroviral therapy in a West African care centre, 2003–2008. *BMC Infect Dis* 2013; **13:**607.
7. Abo Y, Zannou Djimon M, Messou E, *et al*. Severe morbidity after antiretroviral (ART) initiation: active surveillance in HIV care programs, the IeDEA West Africa collaboration. *BMC Infect Dis* 2015; **15:**176.
8. Lewden C, Drabo YJ, Zannou DM, *et al*. Disease patterns and causes of death of hospitalized HIV-positive adults in West Africa: a multicountry survey in the antiretroviral treatment era. *J Int AIDS Soc* 2014; **17:**18797.
9. Seyler C, Anglaret X, Dakoury-Dogbo N, *et al*. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Côte d'Ivoire. *Antivir Ther* 2003; **8:**385–393.
10. Seyler C, Messou E, Gabillard D, Inwoley A, Alioum A, Anglaret X. Morbidity before and after HAART initiation in Sub-Saharan African HIV-infected adults: a recurrent event analysis. *AIDS Res Hum Retroviruses* 2007; **23:**1338–1347.
11. Anglaret X, Minga A, Gabillard D, *et al*. AIDS and non-AIDS morbidity and mortality across the spectrum of CD4 cell counts in HIV-infected adults before starting antiretroviral therapy in Cote d'Ivoire. *Clin Infect Dis* 2012; **54:**714–723.
12. Ciaffi L, Koulla-Shiro S, Sawadogo A, *et al*. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. *AIDS* 2015; **29:**1473–1481.
13. WHO. International Classification of Diseases (ICD). 2015. (Accessed 6 June 2015.) Available from http://www.who.int/classifications/icd/en/
14. (CDC) CfDC. Extension of public comment period for revision of HIV infection classification system and expansion of AIDS surveillance case definition. *MMWR Morb Mortal Wkly Rep* 1992; **40:**891.
15. ANRS. Pays en développement - préparer la recherche - déclaration des événements. (Accessed 06 June 2015.) Available from http://anrs.fr/Rubriques-transversales/Outils-pour-la-recherche/Pays-en-developpement/Preparer-la-recherche/Declaration-des-evenements
16. Anglaret X, Messou E, Ouassa T, *et al*. Pattern of bacterial diseases in a cohort of HIV-1 infected adults receiving cotrimoxazole prophylaxis in Abidjan, Côte d'Ivoire. *AIDS* 2003; **17:**575–584.
17. Luz PM, Bruyand M, Ribeiro S, *et al*. AIDS and non-AIDS severe morbidity associated with hospitalizations among HIV-infected patients in two regions with universal access to care and antiretroviral therapy, France and Brazil, 2000-2008: hospital-based cohort studies. *BMC Infect Dis* 2014; **14:**278.
18. Flateau C, Le Loup G, Pialoux G. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect Dis* 2011; **11:**541–556.
19. Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ. The expanding role of co-trimoxazole in developing countries. *Lancet Infect Dis* 2015; **15:**327–339.
20. Anglaret X, Chêne G, Attia A, *et al*. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet* 1999; **353:**1463–1468.
21. Wiktor SZ, Sassan-Morokro M, Grant AD, *et al*. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet* 1999; **353:**1469–1475.
22. Campbell JD, Moore D, Degerman R, *et al*. HIV-infected ugandan adults taking antiretroviral therapy with CD4 counts >200 cells/μL who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. *Clin Infect Dis* 2012; **54:**1204–1211.
23. WHO. Guide national de prise en charge des personnes vivant avec le VIH/SIDA - Cameroun. (Accessed 19 June 2015.) Available from http://www.who.int/medicines/areas/coordination/cameroon_stgs_avrs.pdf

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